REMARKS

THE CLAIM AMENDMENTS

Claims 1-51, as amended, are currently pending in this application for the Examiner's review and consideration. In an effort to put the pending claims in condition for allowance, independent claims 1, 21 and 47 have been amended to include the feature that the injectable composition and/or microspheres of the present invention are injected into the non-dermal tissue of the mammal during the tissue bulking recited in each of the claims. Support for the claim amendments can be found in the specification, *e.g.*, at page 11, lines, 12-17; page 20, lines 19-29; and page 21, lines 7-14. As no new matter is added by these amendments, Applicants respectfully request their entry into the record of this application at this time.

BRIEF SUMMARY OF THE INVENTION AND THE ARGUMENT

The present invention relates to an injectable composition, method and kit suitable for tissue bulking that comprises biocompatible, swellable, hydrophilic, non-toxic and substantially spherical microspheres and a biocompatible carrier. The claimed invention further requires that the composition or the microspheres be injectable into the non-dermal tissue of a mammal through needles of about 18 to 26 gauge and that the microspheres swell to a predetermined size after injection. Therefore, not only does the present invention relate to a specific type of microspheres that have never been used for tissue bulking purposes as presently claimed, but the invention also claims different ways of employing the unique microspheres in tissue bulking purposes, such as injectable composition, method of treatment and kit.

The Examiner has rejected the claims under 35 U.S.C. § 103(a) as being obvious over references by Rhee, Hubbard, Boschetti, Hori and Vacanti. Applicants respectfully submit that the rejection has now either been obviated by claim amendment or been overcome as set forth below.

Neither Rhee nor Hubbard disclose or suggest a composition, method, or kit for tissue bulking that comprises biocompatible, swellable, hydrophilic, non-toxic and substantially spherical microspheres, as recited in the presently claimed invention. In her reasons for the rejection, the Examiner has made incorrect and/or over simplified statements regarding Rhee, Hubbard and the present invention that result in erroneous conclusions. In fact, not only Rhee and Hubbard, alone or in combination fail to suggest the present invention, the references actually teach away from the present invention by requiring different materials than that of the present invention.

Boschetti, Hori and Vacanti, whether alone or in combinations, fail to remedy the deficiencies of Rhee and Hubbard. Furthermore, the Examiner's rejection based on Boschetti and Hori has been obviated, since the amended claims have made it clear that the tissue bulkings recited therein refer to situations wherein the microspheres are injected into the non-dermal tissues of the mammal.

THE REJECTION UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 1-51 were rejected by the Examiner under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,922,025 to Hubbard ("Hubbard") and U.S. Patent No. 5,550,187 to Rhee et al. ("Rhee"), in view of U.S. Patent No. 5,648,100 to Boschetti *et al.* ("Boschetti"), Japanese Patent No. JP 06-056676 to Shinichi Hori ("Hori"), and U.S. Patent No. 5,855,610 to Vacanti *et al.* ("Vacanti") for the reasons set forth on pages 2-3 of the Office Action. Applicants respectfully traverse this rejection.

Rhee discloses a method for preparing crosslinked biomaterial compositions for use in tissue augmentation and a method for effecting tissue augmentation. Both methods require mixing a biocompatible polymer with a dry crosslinking agent to *initiate* crosslinking between the polymer and the agent and delivering the mixture into either a mold or the tissue site in need of augmentation. *See, e.g.,* Rhee at col. 4, lines 2-21. So, it is inaccurate to simply state, as the Examiner does on page 2 of the Office Action, that Rhee is drawn to a composition for tissue bulking comprising biocompatible hydrophilic polymers, since Rhee

requires that the biocompatible polymer be mixed with a dry crosslinking agent before being used as tissue augmenting materials or before being made into tissue augmenting materials.

Moreover, Rhee, does not disclose or suggest a composition, method, or kit for tissue bulking that comprises biocompatible, swellable, hydrophilic, non-toxic and *substantially spherical microspheres*, as recited in independent claims 1, 21, and 47 of the present application. In fact, the disclosure of Rhee is silent as to any aspect of either a microsphere or a swelling material as an injectable material, as recited in the present invention. Therefore, it is not correct to simply state, as the Examiner does on page 2 of the Office Action, that the present invention is drawn to a composition for tissue bulking comprising biocompatible hydrophilic polymers, since the claimed invention recites more features.

Furthermore, Rhee actually *teaches away* from the present invention. Rhee discloses a method of preparing crosslinked biomaterial compositions that is "user-friendly" to the physician because the method provides *in situ* crosslinking biocompatible polymers with dry crosslinking agent. *See, e.g.*, Rhee at col. 3, line 65 - col. 4, line 21. According to Rhee, the mixture of the biocompatible polymer and the dry crosslinking agent is either extruded into a mold to form implants of desired shape and size or injected, after initiation of crosslinking, into the tissue. *See, e.g.*, Rhee at col. 3, line 65 - col. 4, line 21 and col. 14, line 53 - col. 15, line 64. Moreover, Rhee requires that the mixture must be extruded from the syringe before complete crosslinking has occurred between the biocompatible polymer and the crosslinking agent. *Id.* at col. 15, lines 8-10. Thus, what Rhee discloses is a method in which no solid implant material, not to mention the specific microspheres claimed in the present invention, is present in the composition.

To the contrary, the present invention, as recited in the amended claims, requires that the microspheres, which are solid, be injected into the tissues to serve as solid implants, without any "dry crolinking agents" or "in situ crosslinking," as required by Rhee. Therefore, a person of ordinary skill in the art not only would fail to achieve the present invention based on Rhee, but would actually be taught away from the present invention.

Hubbard discloses an augmentation material comprising smooth rounded, substantially spherical, particles of a finely divided *ceramic* material that is substantially non-resorbable. *See* Hubbard at col. 5, lines 1-3 and lines 36-37. Hubbard, however, does not disclose a composition, method, or kit for dermal augmentation that comprises biocompatible, *swellable, hydrophilic*, non-toxic and substantially spherical *microspheres*, as recited in independent claims 1, 22, and 47 of the present application. Hubbard further fails to disclose or suggest a composition that comprises microspheres that swell to a predetermined size after injection, much less microspheres that swell after injection up to four times their pre-injection size, as presently claimed. In fact, the finely divided ceramic particles disclosed in Hubbard are, by definition, the direct opposite of the *swellable and hydrophilic* characters of the microspheres required by the present invention.

It is not correct to simply state, as the Examiner does on pages 2-3 of the Office Action, that the present invention is "drawn to compositions for tissue bulking spherical particles of biocompatible material." Applicants respectfully draw the Examiner's attention to page 10, lines 9-15 of the specification, where "microspheres" are defined as "polymer or combination of polymers made into bodies of various sizes." In other words, Hubbard is silent with regard to swellable, hydrophilic, and polymer, all of which are required by the presently claimed invention.

Hubbard, too, actually teaches one of ordinary skill in the art away from the claimed invention, by its disclosure of a biocompatible composition made from ceramic particles of calcium hydroxyapatite or calcium phosphate-based or alumina-based materials (*see* Hubbard at col. 5, lines 46-52; col. 7, lines 27-36), which cannot be swellable, hydrophilic, or a polymer, as required by the present invention.

Boschetti discloses microspheres useful for therapeutic vascular occlusions and injectable solutions containing the microspheres. Boschetti, however, fails to remedy the deficiencies of Rhee or Hubbard in that it does not disclose or suggest a composition that comprises microspheres that swell to a predetermined size after injection. Thus, alone or in any combination with Rhee and/or Hubbard, Boschetti fails to disclose or suggest all the instantly claimed elements.

As stated in the specification, "tissue bulking" within the context of the present invention refers to any change of the natural state of a mammal's non-dermal tissue due to external acts or effects. *See*, specification at page 11, lines, 12-17. While this definition of "tissue bulking" is broad, the specification also contains specific embodiments wherein the "tissue bulking" is achieved by injecting microspheres of the present invention into the tissues of a mammal. *See, e.g.*, specification at page 20, lines 19-29; and page 21, lines 7-14. Furthermore, the amended claims have made it clear that the tissue bulkings recited therein refer to situations wherein the microspheres are injected into the non-dermal tissues of the mammal.

Therefore, Boschetti actually teaches away from the claimed invention through its disclosure that the microspheres be placed within the lumen of blood vessels and used as emboli for therapeutic vascular occlusion (*see* Boschetti at col. 1, lines 10-25). On the other hand, the present invention, as recited in the amended claims, requires that the microspheres be injected *into* the tissues being bulked.

Hori, like Boschetti, teaches away from the claimed invention through its disclosure that granules of a water-absorbing resin be used as emboli in occlusions or embolizations in blood vessels (*see* Hori Abstract). There is no disclosure or suggestion in Hori that microspheres, as recited in the amended claims, being used for tissue bulking.

Furthermore, one of ordinary skill in the art would not have had a motivation to combine the Hori and Boschetti references with Rhee and/or Hubbard. Hori and Boschetti both involve compositions for emboli in blood vessels, whereas the disclosures of Rhee and Hubbard involve tissue augmentation. Applicants maintain that one of ordinary skill in the art would not have considered their disclosures relevant enough to each other to combine them.

Applicants also submit that one of ordinary skill in the art, even if somehow motivated to combine these disparate prior art references, would nevertheless have had no reasonable expectation of success in achieving the claimed invention. In order to achieve the claimed invention, the water-absorbing ability of the Hori composition would have to have been combined with the hydrophilic character and the ability to form a sterile particulate

suspension without aggregates, as taught by Boschetti. That combination being difficult to achieve in and of itself, one of ordinary skill in the art would have also had to introduce the biocompatibility, non-toxicity, and substantially spherical nature of the ceramic particles of Hubbard to the emboli of Boschetti and Hori, which are disclosed for a totally different application.

Vacanti discloses the use of autologous cells seeded in a fibrous matrix and a cell-matrix structure that, after implantation into certain tissue, results in improved yields of engineered tissue. Applicants submit that this disclosure does not remedy the deficiencies of the other cited references. Applicants further submit that the combination of these five references is even more disparate, reducing even further any possible motivation of one of ordinary skill in the art to combine the Vacanti disclosure, being drawn to tissue engineering and cell regrowth, the disclosures of Rhee, relating to *in situ* crosslinking of biocompatible polymers, Hubbard, involving tissue augmentation through ceramic microspheres, and Hori and Boschetti, which relate to therapeutic occlusions of blood vessels. Further, there is even less reasonable expectation of one of ordinary skill in the art to succeed in achieving the claimed invention because of the disparate references.

For the foregoing reasons, Applicants submit that a *prima facie* case of obviousness has not been made and, in any event, cannot be maintained against the amended claims. Applicants therefore respectfully request that this obviousness rejection be reconsidered and withdrawn.

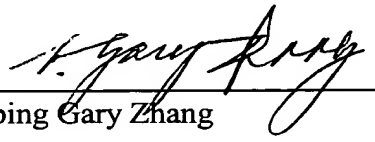
CONCLUSION

Applicants respectfully submit that the obviousness rejections of claims 1-51 are either inapplicable to the amended claims or have been overcome and that the claims, as amended, are now in condition for allowance. Should the Examiner disagree, Applicants respectfully request a personal or telephonic interview to discuss any remaining issues and to expedite the eventual allowance of this application.

No fee, except for Notice of Appeal and the Petition for Extension of Time submitted herein, is believed to be due for this submission. Should any additional fee be required, however, please charge the required fee to Pennie & Edmonds Deposit Account No. 16-1150.

Respectfully submitted,

Date March 25, 2002



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Enclosures